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### Remarks

The above Amendments and these Remarks are in reply to the Office Action mailed April 16, 2003.

Claims 32 and 36 have been amended to correct typographical errors, and thus are not narrowing amendments. Claims 38-44 have been amended to correct antecedents and are asserted to be not narrowing amendments.

Claims 11-16, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C. §102(b) as anticipated and/or obvious under 35 U.S.C. §103 by Sara et al. (EP 0366638; "Sara 1") alone or in combination with the instant specification at pages 1-2 to demonstrate inherency e.g., damage/loss of glial cells resulting from [due to] neural damage/injury e.g., from asphyxia/ischemia/hypoxia/stroke, and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons. Office Action, page 4, paragraph 7. Additionally, "Thus, the reference treatment of neurodegenerative/neurocatabolic disease states and ischemic brain damage (e.g., stroke and asphyxia) addresses the treatment of injuries or disease which result in neural cell death." Office Action, page 7 bridging to page 8. Applicants respectfully traverse the rejections.

## I. Anticipation

Applicants submit that Sara 1 does not anticipate, either expressly or inherently, the instant claims.

MPEP 2131 states:

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference [references omitted]. The identical invention must be shown in as complete detail as is contained in the ... claim [reference omitted]. Emphasis added.

## **Express Anticipation**

Sara 1 does not disclose "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease comprising the step of administering to said mammal a neuroprotective amount of . . GPE, "and therefore doesn't expressly disclose "each and every element as set forth in the claim" as required. The Examiner's statement "[t]hus, the reference treatment of

neurodegenerative/neurocatabolic disease states and ischemic brain damage (e.g., stroke and asphyxia) addresses the treatment of injuries or diseas—which result in neural cell death" is unclear. Applicant does not understand whether the term "addresses" was intended to mean "anticipates." Clarification is requested. However, regardless of the meaning of the term "addresses," Applicants assert that altering neurotransmitter release induced by cellular depolarization does not necessarily include treating "injuries or disease which results in neural cell death." Thus, Applicants respectfully submit that Sara 1 does not expressly disclose each and every element of claim 11.

## **Inherent Anticipation**

Applicants submit that Sara 1 does not inherently anticipate the instant claims. MPEP 2112 states:

To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Emphasis added.

Firstly, Applicant's claims are drawn to "methods for treating" and not to "compositions." Applicants note that a claim is drawn to an "invention" and that invention requires a conception and reduction to practice. Applicants note that the discovery of a new effect or new use of a known composition results in a new "conception" and thus a new "invention" that is not necessarily unpatentable. Thus, Applicants' discovery of "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease comprising the step of administering to said mammal a neuroprotective amount of ... CiPE" is not necessarily rendered unpatentable by prior art disclosing either GPE or other uses of GPE.

## Missing Elements Defeat Anticipation by Inherency

Applicants respectfully submit that there are elements missing from the prior art necessary to link a "neuromodulator" effect of Sara 1 and "neuroprotective" effects of the instant application. Specifically, the words "neuromodulator" and "neuroprotective" do not have the same plain meanings, and are used

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differently in the documents themselves. Applicants enclose as Appendix I, copies of relevant pages of the Random House Unabridged Dictionary (Second Edition).

## Plain Meanings of "Neuromodulator" and "Neuroprotective"

The term "neuromodulator" is a compound word made of the prefix "neuro," which is understood by persons in the art to refer to neurons. The remainder of the word is "modulator" which is subject to definition by referring to its plain meaning as defined in dictionaries.

The Random House Unabridged Dictionary (Second Edition) defines "modulator" to mean:
"A person or thing that modulates."

The word "modulate" means:

(1) to regulate by or adjust to a certain measure or proportion; soften; tone down. (2) to alter or adapt (the voice) according to the circumstances. (3) Music (a) to attune to a certain pitch or key. (b) to vary the volume of (tone). (4) Telecommunications: (a) to cause the amplitude, frequency, phase, or intensity of (a carrier wave) to vary in accordance with a sound wave or other signal, the frequency of the signal wave usually being very much lower than that of the carrier. . Emphasis added.

Likewise, the words "neuroprotective" and "neuroprotection" are compound words consisting of the prefix "neuro" and the remainder being either "protective" or "protection." The Random House Unabridged Dictionary (Second Edition) defines "protection" to mean:

(1) the act of protecting or the state of being protected; **preservation** from injury or harm. (2) a thing, person, or group that protects: This vaccine is a protection against disease. . . ." Emphasis added.

Applicants note that the dictionary does not list either as a synonym of the other. Thus, the two terms "modulate" and "protect" have different plain meanings.

Applicants submit that the word "neuromodulate" as used in Sara 1, most closely fits with the definition above "to regulate by or adjust to a certain measure or proportion." The Experiments described in Sara 1 demonstrate that GPE can "regulate or adjust" the function of neurons in brain slices by increasing or inhibiting the release of acetylcholine or by increasing the spinal reflex response.

Applicants also submit that the meaning of the claim limitation "neuroprotective amount of ... GPE" means an amount of GPE that is "neuroprotective." Applicants further submit that the definition described above applies to the claim language: "preservation from injury or harm" or "a thing. . that protects."

The Terms "Neuromodulator" and "Neuroprotective" are Used Differently By Sara and by Applicants

Sara 1 uses the term "neuromodulator" in relation to results of acute, in vitro studies on brain slices (e.g., Example 2), in which GPE "is a modulator of neural function, thereby stimulating or inhibiting neural activity." Col. 1, lines 36-37; emphasis added. Sara 1 also discloses results of studies showing potentiation of spinal cord reflexes by GPE. Applicants assert that this use of "neuromodulator" is very close to the plain meaning above, namely "to regulate [neurotransmitter release or spinal reflexes] by or adjust to a certain measure or proportion [e.g., by GPE]."

In contrast, Applicants use the term "neuroprotective" refers to inhibition of cell death, as pointed out in claim 11: "A method for protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease comprising the step of administering to said mammal a neuroprotective amount of . . . GPE..." Emphasis added. Applicants submit that their use of "neuroprotection" is close to the above definition: "the act of protecting or the state of being protected; preservation from injury or harm. (2) a thing, person, or group that protects: This vaccine is a protection against disease. . . ." [Emphasis added, italics in original.]

For Sara 1 to inherently anticipate the instant claims, persons of ordinary skill would have to believe that both increasing and decreasing neurotransmitter release are necessarily linked to "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." If the Examiner is aware of any evidence of such a reasonable belief, he is requested to provide such evidence, through either a prior art reference if available, or an Affidavit or a Declaration.

Further, Applicants invite consideration of what is not disclosed in Sara 1. Although Sara 1 discusses potential uses of GPE to treat dementias, Sara 1 does not provide an enabling disclosure of any such uses. Sara 1 discloses no experiments on neural survival. Sara 1 discloses (1) no *in vivo* experiments

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in which GPE was used, (2) no long-term studies of any effect of GPE, (3) no experiments in which neural survival in vivo or in vitro was measured, and (4) no link between acute in vitro studies on acetylcholine release or spinal cord reflexes and survival of any cell type. Further, (5) none of the studies were described as being on brain slices from any animal that had been subjected to neural damage or disease. Thus, Applicants conclude that Sara 1 did not describe any conception and reduction to practice of any "neuroprotective" effect of GPE, and therefore cannot anticipate the instant claims.

Finally, the Examiner has provided no evidence that necessarily links "stimulating or inhibiting neural activity" with "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease" as in claim 11. [Emphasis added.]

Therefore, Applicants submit that Sara 1 cannot inherently indicate that neuromodulation is useful for "protecting glial cells or non-doparninergic neural cells in a mammal against death from neural injury or disease" Although it may be possible that such an effect exists, such a **possibility** cannot sustain a rejection based on inherency. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." MPEP, Id. Thus, Applicants submit that a *prima facie* case for anticipation has not been made.

In light of the dearth of enabling disclosure about roles of GPE on neuroprotection, Applicants submit that Sara 1 cannot anticipate the instant claims.

## II. Obviousness

## A. Sara

Claims 11-17, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C. §103 as obvious over Sara (Sara 1).

To establish a prima facte case for obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination

and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

Applicants respectfully submit that the instant claims cannot be rendered obvious by Sara 1. As described above, Sara 1 discloses that GPE either "stimulates or inhibits" neural activity and can potentiate spinal cord reflexes. However, Sara 1 neither teaches nor suggests that GPE can be effective in "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." [Emphasis added.] Applicants therefore submit that Sara 1 cannot render the instant claims obvious.

Thus, at best, the experiments disclosed in Sara I provide an "invitation to experiment" on possible effects of GPE on brain slices from brain-damaged or brain-diseased animals, but could not have provided a reasonable basis to conclude that acute effects of GPE on neurotransmitter release inherently discloses any property of GPE to promote "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." Rather, for Sara 1 to render the instant claims obvious, both potentiation and inhibition of acetylcholine release would have to relate to "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease". No link between neurotransmitter release and either disease or cell death was made in Sara 1, nor was there any disclose of conception or understanding that intervention using GPE could result in decreased neural cell death (neuroprotection).

Regarding the fact that a *prima facie* case for obviousness requires a "motive to modify the reference" and "reasonable likelihood of success," Applicants note that a subsequently published article by Sara ("The Biological Role of Truncated Insulin-like Growth Factor-1 and the Tripeptide GPE in the Central Nervous System" Annals of the New York Academy of Science; pp. 183 - 191 (1991); "Sara 2"; copy enclosed in Appendix II) addresses similar issues as in the Sara EP 0366638 ("Sara 1") but actually teaches away from Applicants' claims. In particular, Sara 2 states:

Extensive in vivo studies have not revealed any growth-promoting activity of GPE.... As shown in Figure 4, no significant growth effects, including tail length and organ weights, were observed. Page 187, middle of first full paragraph.

Thus, Applicants submit that at the time of publication of Sara 2, the first inventor of Sara 1 (Sara) could not have had a reasonable belief that GPE could be a growth modulator, and thus that there would be neither a motive to try nor a reasonable likelihood of success at achieving the Applicants' invention. In the absence of a reasonable belief by the primary inventor, Applicants submit that no person of ordinary skill could have such a reasonable belief. Applicants submit that both Sara 1 and Sara 2 considered GPE to be an agent that acted on neurotransmitter receptors and not as a growth promoting hormone. Because Sara 1 was silent about any effects of GPE to promote "protecting glial cells or non-doparninergic neural cells in a mammal against death from neural injury or disease," Applicants submit that at the time of publication of Sara 1, there was neither motive nor a reasonable belief that GPE could so act.

Rather, Applicants respectfully submit that the motive and reasonable likelihood of success were provided by the Applicant's own instant disclosure.

## B. Sara in View of Sibalis

Claims 11-17, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C.§103 over Sara (Sara 1) in view of Sibalis (U.S. 5,032,109; "Sibalis").

Applicants incorporate herein the discussions presented above for Sara 1.

The Examiner stated that Sibalis teaches transdermal delivery of "polypeptides containing about three to 20 alphaamino acid units." However, Applicants can find no teaching in Sibalis and Sara 1 together of any method for "protecting glial cells or non-dopaminergic neural cells in a manuful against death from neural injury or disease." Thus, the combination of Sara 1 and Sibalis does not disclose all the limitations of the pending claims with a reasonable likelihood of success, and thus cannot render Applicants' claims obvious. Applicants therefore urge the Examiner to reconsider the rejection and find the claims allowable.

## C. Sara in View of Gluckman

Claims 11-16 and 18-46 stand rejected under 35 U.S.C. §103 over Sara (Sara 1) in view of Gluckman (WO 93/02695; "Gluckman").

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Applicants incorporate herein the discussions presented above for Sara 1.

The Examiner stated that Gluckman teaches "a method for treatment or prevention of CNS damage caused by neurodegenerative disease and trauma which primarily causes damage to glia and/or other non-cholinergic cells in the CNS." Office Action, page 9, bottom paragraph. The Examiner also stated "It is noteworthy that the Gly-Pro-Glu peptide, as presently claimed, is derived from the N-terminal three amino acids of IGF-1 peptide." Office Action, page 10 bottom of first paragraph.

Applicants note that Gluckman does not disclose "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of ... GPE ..." as in claim 11. Nowhere in either Sara 1 nor Gluckman, nor in the combination of Sara 1 and Gluckman together, is any teaching of the use of GPE as in claim 11. Thus, the combination of Sara 1 and Gluckman does not disclose all the limitations of the pending claims with a reasonable likelihood of success, and thus cannot render Applicants' claims obvious. Although GPE is the N-terminal tripeptide of IGF-1, both Sara 2 and Gluckman teach away from GPE as a neuroprotective agent. First, Gluckman teaches that IGF-1 is neuroprotective (e.g., see Abstract and Summary of the Invention, page 3, first paragraph). Next, Sara 2 states: "The aminoterminal tripeptide of IGF-1, GPE, displays a different range of biological actions compared to truncated IGF-1. These effects are not mediated by IGF-1 receptors. As shown in Figure 3, GPE fails to cross-react with the IGF-1 receptor and does not influence the binding of either intact or truncated IGF1 to the receptor." Page 187, middle paragraph, middle section. Thus, Applicants submit that one or ordinary skill in the art would view Sara 1 in the same light as Sara 2, and when combined with Gluckman, would provide no motive to nor a reasonable believe in the success of, any study to determine whether GPE had neuroprotective properties.

Rather, Applicants submit that the instant disclosure provided the link between IGF-1, GPE and "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of ... GPE ..." as in claim 11. "To date, there has been no enabling reference in the prior art to the manipulation of the cleaved tripeptide GPE itself to prevent or treat CNS injury or disease leading to CNS damage *in vivo*." Page 3, third paragraph. Using such hindsight reconstruction to argue for unpatentability is impermissible under 35 U.S.C. §103, the MPEP

and case law. Applicants therefore urge the Examiner to reconsider the rejections and find the claims allowable.

## III. Conclusions

Applicants respectfully submit that there is insufficient showing that Sara 1 either expressly or inherently anticipates or renders the instant claims obvious and that no *prima facte* for either rejection has been made. Applicants respectfully request the Examiner to provide the missing evidence necessary to make a *prima facte* showing of either anticipation or obviousness. In the absence of such evidence, either through citation of a publication or through an Affidavit or Declaration, Applicants request the Examiner to reconsider the rejections and find the claims allowable.

Further, Applicants conclude that no combination of Sara 1, Sibalis or Gluckman taught or suggested, with a reasonable likelihood of success, all limitations of the instant claims, and therefore, that no combination of those references renders the instant claim obvious. In fact, Sara 2 actually taught away from the instant claims. Because Sara 2 was published after Sara 1, Applicants conclude that any interpretation of Sara 1 to teach "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of ... GPE ..." is not supported.

In light of the above, it is respectfully submitted that all of the claims now pending in the subject patent application should be allowable, and a Notice of Allowance is requested. The Examiner is respectfully requested to telephone the undersigned if he [she] can assist in any way in expediting issuance of a patent.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit

Account No. 06-1325 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: July 10, 2003

D. Benjamin Borson, Ph.D.

Reg. No. 42,349

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## APPENDIX I

## Copies of Relevant Pages from

Random House Unabridged Dictionary (Second Edition)

# RANDOM HOUSE

proper at the processing

# DICTIONARY

Second Edition

विकेरिकेर हार कर केरेरोड़िक होना होते. एकर मुनर्का केर किर आक्रार एक सुन्द स्केर कर है कि रहते हैं कर उन है है

o-der-sohn-Beck-er (mo'den zön hek/en), n. Pata ı (pou/lä), 1878–1907, German painter

I (pou/la), 1878-1907, German painter

Od-e5t (mod/ist), edj. 1. having or showing a modrate or humble estimate of one's merits, importance,

rete in humble estimate of one's merits, importance,

retersions 2 free from estentation or showy extrava
nuce a modest house 3. having or showing regard for

re decencies of behavior, speech, dress, etc; decent; o
rodest neckline on a dress. 4. limited or moderate in

mount, extent, etc.: a modest increase in salary, [1555.

5; < L modestus restrained, decorous, equiv. to modes
to of "modests restrained, decorous, equiv. to modes
nedos, with the vowel of modus; of moderari to mon
neart, from the same n: stem) + -tus adj. mufflx]

-modest-ly, adv.

RATE, from the same n. stem) + -tus adj. suffly -mod/est-ly, adv.

—Syn. 1. retiring, unassuming. 1. 2. unpretentious nobtrusive. 3. pure, virtuous. Monser, nemust, vatious imply conformity to propriety and decorum, and a istante for anything coarse or loud. Monsey implies a coming shyucas, sobriety, and proper behavior: a modest, self-repecting person. Demuse implies a bashful, ulet simplicity, staidness, and decorum; but can also inicate an assumed or affected modesty: a demuse young horus girl. Pauman suggests an exaggeratedly self-condous modesty or propriety in behavior or convensation fone who wishes to be thought of as easily shocked and the often is intolerant a prudish objection to a harmless emork. —Ant. 3. hold, coarse.

lo-des-to (ma des-tō), n. a city in central California.

bod-es-ty (mod/s stē), n., pl. -ties. 1. the quality of seing modest; freedom from vanity, boastfulness, etc. 2. egard for decency of behavior, speech, dress, etc. 3. implicity, moderation. [1525-35; < 1. modestic, Sec. 400531, -4"]

10d'esty pan'el, a panel across the front of a deak, an, an office deak, designed to conceal the legs of a person seated at it.

**IODFET** (mod'fet'), n. Electronics. modulation-doped ield effect transistor.

iodGk, Modern Greek, Also, Mod. Gk., Mod. Gr.

iodileb, Modern Hebrew, Also, Mod. Hab.

\*\*\*sod-beum (mod'i kem), n. a moderate or small unount He hasn't even a modicum of common sense, 1425-75; late ME < L. n. use of neut. of modicus moderate equiv. to modic, comb. form of modus limit (see MODE') + -cus adj. suffix)

nodifi... modification.

nodi-fricant (mode si kand), n. Grum. a word that s modified, or qualified, by another. In red books, books a modificand. [1825-85; < L modificand. (a thing) be measured or limited, ger. of modificars to wopure to be measured or limited, ger, of modificars to wooter!

nod-li-ca-tion (mod's fi ke'shen), n. 1. an act or instance of modifying. 2 the state of being modified partial alteration. 3. a modified form; variety. 4. Biol. a change in a living organism acquired from its own activity or environment and not transmitted to its descendants. 5. limitation or qualification. 6. Gram. a the use of a modifier in a construction, or of modifiers in a class of constructions or in a language. b. the meaning of a modifier, esp. as it affects the meaning of the word or other form modified. Limitation is one kind of modifiedition. c. a change in the phonological shape of a morpheme, word, or other form when it functions as an element in a construction, as the change of not to -n't in doesn't, d. an adjustment in the form of a word as it passes from one language to another. [1495-1505; < 1. modifications (a. of modification), equiv. to modification (pp.) of modificares, see money) + -ion. -10n!

nod-i-fi-ca-to-ry (mod/s fi ks tar-e, -15n-e).

modificatory (mod/a fi ka tār/ē, -tār/ē), adj. modifying. Also, mod/i+k-cative. [1815-25; < L modificat(us) (see Modification) + -okt']

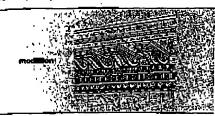
mod/ffied Amer/ican plan/, (in hotels) a system of paying a single fixed rate that covers room, breakfast, and one other meal, usually dinner. Abbr.: MAP Cl. American plan, demi-pansion, Europoan plan.

American para, numerousian, European pears, and a modifice. Inod's fi/srl, n. 1. a person or thing that modifice. 2. Gram. a. a word, phrase, or sentence element that limits or qualifies the sense of another word phrase, or element in the same construction. b. the immediate constituent of an endocentric construction that is not the head. [1575-85; MODIT' + ERT]—Usage. See dangling participle, misplaced modifier.

modifier.

modilier. (mode ft/), v., find fying —u.t. 1. we change somewhat the form or qualities of alter partially symend: to modify a contract. 2. Gram. (of a word phrase, or chuse) to stand in a syntactically subordinate relation to (another word, phrase, or clause). usually with descriptive, limiting, or particularizing meaning be a modifier. In a good man, good modifier mon. 3. to be the modifier of attribute of. 4. to change (a vowel) by umlaut. 5. to reduce or lessen in degree or extent moderate, soften to modify one's demands. —u.i. 6. to be or become modified. (1350-1400; ME modifier < Mf modifier < L modifiedre to impose a rule or pattern, regulate, restrain. See woost, pri) —mod/if/s-ble/sty, mod/f/s-ble-ness. n. — Syn. 1. vary, adjust, shape, reform. 5. Moorry, quality, temper suggest altering an original statement, condition, or the like, so us to avoid anything excessive or extreme. To monry is to after in one or more particulara generally in the direction of lenicacy or moderation to modify demands, rates. To quality is to restrict or limit by exceptions or conditions: to qualify one's pruise.

FDM&L var. 01 "mutulionem, acc. of "mutulio. See MUTULE, -10H)



modifolis (mo di'e les, me-), n., pl. 4l (-li'). Anothe central, conical axis of the cochlea of the ear. [1685-95; < NL, L. pave of a whoel bucket, dripking vessel, equiv. to modifuel a dry measure (perh. deriv. of modus MODE!) + -olus -OLE!] —modifoliar, adj.

mod-ish (mö/dish), adj. in the current fashion; stylish. [1850-60; Mone" + -198"] —mod/ish-ly, adv. —mod/ish-ss, h.

Syn. smart, chic, fashionable, trendy.

mo-diste (mö dēst'; Fr. mô dēst'), n., pl. distes (dēst'; Fr. dēst'). Older Use a female maker of or deslar in women's fashionable attire. (1830–40; < F; see MODE\*, -IST)

Mo-d]es-kā (mō jer/kə), n. He-le-na (hə la/nə), (Hel-ena Opid Modrzajsusska), 1840–1909, Polish actress, in U.S. after 1876.

Mo-doc (mō/dok), n., pl. -docs (esp. collectively) -doc. a member of an American Indian people belonging to the Lutusmian group and ranging from southern Oregon to porthern California.

mo'dock wool' (mo'dok). See territory wool, [apecial use of Monoc]

mod. praesc., (ju prescriptions) in the manner pre-scribed; as directed. (< L modo prosscripto)

Mo-dred (mo/drid), n. Arthurian Romance. the nephew and treacherous killer of Arthur. Also, Mor-dred. Mo-dred

module or a modulus. 2. composed of standardized units module or a modulus. 2. composed of standardized units or sections for easy conservation or flamble arrangements a modulur home; a modulur sofa. 3. Math. (of a lattice) having the property that for any two elements with one less than the other, the union of the smaller element with the intersection of the larger element and any third element of the lattice is equal to the intersection of the larger element with the union of the smaller element and the third element. 4. Computers composed of software or hardware modules that can be altered or replaced without affecting the remainder of the system. —a. 5. something, as a house or piece of familiars, built or organized in self-contained units or sections. 6. a self-contained units or item, as of familiars, that can be combined or interchanged with others like it to create different shapes or designs. [1790-1800; < NL modulāris. See modular arith/metic, arithmetic in which numbers

mod'ular arith/metic, arithmetic in which numbers that are congruent modulo a given number are treated se the same. Cf. congruence (def. 2), modulo, modulus (def. 20). [1955-60]

mod-u-lgr-hty (moj/s lar/i të, mod/ye-), n. the use of individually distinct functional units, as in assembling an electronic or mechanical system. [1935-40; MODULAR +

mod-u-lar-ize (moj/s is riz/), u.t., -ized, -iz-ing, to form or organize into modules, as for flexibility. Also, esp. Brit., mod/u-lar-ise/. [1955-60; MODULAR + -izx] —mod/u-lar-i-ze/tion, h.

mod-u-late (moj/s lat/), u. -isted. -isting. — u.t. 1. to regulate by or adjust to a certain measure or proportions soften; tone down. 2. to alter or adapt (the voice) according to the circumstanced, one's listener, etc. 3. Music a: to attune to a certain pitch or key. b. to vary the volume of (tone). 4. Telecommunications to cause the samplitude, frequency, phase, or intensity of (a carrier wave) to vary in accordance with a sound wave or other signal, the frequency of the signal wave usually being very much lower than that of the carrier. — u.i. 5. Telecommunications, a. to modulate a carrier wave. b. CB Slang. to talk; visit: Enjoyed modulating with you. CB Slang to pass from one key to another: to modulate obruptly from A to B flat. [1550-60; < L modulates (ptp. of modulari to regulate (sounds), set to music, play an instrument). See MODULE. -arri! — modula-bility (moj/s is bil/i tè), h. — mod/u-la-tiva, mod-u-la-bility (moj/s is tör/s, -tör/s), adj.

— Syn. 2. temper, control. mod-u-late (moj/ə lāt/), v., -lat-ed, -lat-ing.

mod-u-la-tion (moj's la/shan, mod'ya-), n. 1. the act of modulating. 2 the state of being madulated. 3. Music transition from one key to another. 4. Gram, a, the use of a particular distribution of stress or pitch in a construction, as the use of rising pitch on here in John is here? b, the feature of a construction resulting from such use. (1350-1400; ME < L modulation. (a. of modulation (property of the construction resulting from the construction because the construction resulting from the construction resulting from the construction of the construction of

modulating a carrier wave. [1490-1500; < L modulator, even

mod-tile (moj/col), n. 1. a separable component, fre-

**2**020

any two operators and any group element the having the first operator act on the element accord element; and the second operator act on delement is equal to the result of having a stator, formed by adding or multiplying the tors, act on the first element. Cf. ring! (de Computers. 3. part of a program that perform function, b. an interchangeable, plug-in hard [1555-65; C. modulus; see Montus.]

modulus 6 is congruent to 11, modulo & NL modulo, abl. of L modulus MODULUS] with re

modulus (moj'e lad, n. pl. if (l), 1. Pheficient pertaining to a physical property. I that number by which the logarithms in one; multiplied to yield the logarithms in another. ity by which two given quantities can be yield the same remainders. c. See absolu [1555-65; < L: a unit of measure; see scort.

mod'ulus of elastic/ity. Physics. any of efficients of elasticity of a body, expressing th tween a stress or force per unit area that acts the body and the corresponding fractional d caused by the stress. Also called coefficient ity, plastic modelus. [1800-10]

mod'ulus of rigid'ity, Physics. See shear (1875-801

modulus of tor/sion, Physics. See shear modes openand (modes openand modes openand openand modes of penand), pl. mod openand openand

modus vi-van-di (mö/das vi ven/da, -di),
vi-van-di (mö/da vi ven/da, mö/di vi ven/di,
ner of living; way of life; lifestyle. 2. a tem
rangement between persons or parties pendir
ment of matters in debate. [1875-80 < L moo
mode of living]

Moe (mo), r. a male given name, form of

Moe-bi-us (mæ/bē ss, mā/-, mō/-), n. Aug nand. See Möblus, August Ferdinand.

Moe-rae (me/re), n.pl. Class. Myth. the Fat Moe-si-3 (mē'ahē a), n an ancient country rope, S of the Danube and N of ancient Thrace educia: later a Roman province.

Moe-sp-goth (mē'as goth', -sa-), n one of tianized Gotha who settled in Moesia in the 4

A.D.

Mos-so-goth-le (me'so goth'ik, -se-), adj. taining to the Mossogoths or their language coth + -sc)

mo-fette (m5 fst/; Fr. m5 fst/), n. 1, a not nation, consisting chiefly of carbon dioxide from the earth in regions of nearly extinct vivity. 2 one of the opening or fissures from emanation issues. Also, mor-fette/. [1815-25 moffetta (Neapolitan mu/fsto), equiv. to maff it mofs) mould (< Langebordic ef. G Muff : MHG milifeln to give off a foul smell) + -eft

mog! (mog), b. mosged, mog.ging. Dial. move on, depart, or decamp (usually fol by 2. to walk or move along gently, slowly, an —u.t. 3. to cause to go from one place b [1685-75; M(ove) + (J)oc!]

mog2 (mog), n. moggy. [by shortening]

Mo-ga-di-shu (mô/gā dō/shoo), n. a seap the capital of Somalia, in the S purt. 400,000. It ga-di-sclo (mô/gā dē/shò).

Mog-a-dor (mog'e darr, -dor'; Fr. mô ga di former name of Essaouira. 2. (Lc.) Also, mo, a ribbed fabric of silk or rayon warp and cotte filling, used for necktles.

Mo-gon Da-vid (mô/gon dâ/vid; Seph. Hel dã v8ð'; Ashk. Heb. mô/gon dô/vid), Jude Star of David. [1900-05]

mog-gy (mog'e), n., pl. gies. Brit. Inform Also, mog. [1815-25; said to be orig. Cocknay derivations from dial. (W Midlands) Moggy po a calf, or from personal name Maguz, are di Moghul (mō/gəl, -gul, mō gul/), n., adj. M

Morgi das Gru-zes (mõõ zhē/ dãa krōō/z in SE Brazil, E of São Paulo, 111,654.

mogoi-la-li-3 (moj's lä/ls a, -lal'ye), n. any feet, as cuttering or atsumering. Also, mollisi 80; < Gk mogiki(as) hardly telking (mogics) culty + lálos babbling) + -ia -la]

Mo-gi-lev (mo/gi laf'; Russ mə gyi lyôf'), n E Byelorussia (Belarus), on the Dnieper. 359,(

mo-go (mo'go), n. pl. -gos. Australian. hatchet used by the Aborigines. [1815-25;

Mo-gol-lon (mo'go yōn'), a 1. an extensi-or mess in central Arizons, the southwestern the Colorado Plateau. 2. a mountain range Mexico. —odj. 3. Archaeol of or pertaining to indian culture of southeastern Arizona and sor New Mexico 100 a.c.—a.p. 1000, characteriz houses also used for burial and a distinctive white pottery decorated with human and snir

e prospectus carefully. 2. a bruchure of other hearthing the major features, attractions, or a place, institution, or business to prospective mb, owners, or members. [1770-80; < L proook, view, equiv. to prespect, a of prespector + espicers, comb. form of specers to look) + of v. action)

(pros/per), u.i. 1. to be successful or fortu-i financial respects; thrive; flourish. —u.t. 2. make successful or fortunate. [1425-75; late en < L prospertire to make happy, deriv. of BOSPEROUS]
See succeed. — Ant. 1. fail.

ty (pro sport ta), n., pl. 1802. 1. a successing, or thriving condition, esp. in financial of fortune. 2. prosperities, prosperous cir[1176-1225, ME prosperite < OF < 1, pro2 PROSPEROUS, -TTY]

(pros/ps ro/), a. (in Shakespeare's The exiled Duke of Milan, who is a magician. e exist true of anima, the string or characteristics or good fortune; flourishing or prosperous business. 2 well-to-do or resperous family. 3. favorable or propiniona to ME < L prosperus]—pros/per-ous-ly, per-ous-noss, h thriving. 2 we

2 wealthy, rich. 8, fortunate.

2 (Gk pros/fo nā; Eng pros/fo rā', -18r a), h. antidoren. [1870-76] < Gk prosphorá an a bringing to, applying, equiv. to pros- to-ré something carried (verbid of phérein to

on (Gh. pade/fo adu; Eng. pros/fe ron/, kastern Ch. an uncut lost of altar bread be-secrated. (< Gk prispheron, n. use of neut. s useful. fitting, deriv. of prospheri reas-

a), u.i. Scot. and North Eng. to exhibit pride ss; put on airs. [perh. Scots var., in v. use. —pross/er, n. —pross/y, adj.

i), n. Slang. prostitute. [by shortening and

ros/ar), n. Gabriel, 17757-1800, U.S. leader ful slave revolt.

) interi prosit [by contr.]

clin (pres'ts st'klin), n. Biochem. a pros-sH20, that specifically inhibits the forma-l clots. [1975-80; frosta(tr) + cycl(n;) + model of frostaglandis]

modin (pros/ts gian/dia), n. 1. Biochem, so of unsaturated fatty acids that are in1 contraction of smooth muscle, the control ion and body temperature, and many other functions. 2. Pharm. any commercial of this substance. [1935-40; prosta(TE) + a-din (pros/to glan/din), n

ro'stas), n., pl. pro-sta-des (pro ats/dsz), al archivecture) on antechamber or vicati-a classical temple) the area included be-ades. (< Gk prosies lit., that which stends ostasse)]

(pro sia/mia), n., pl. -see (-sez). (in a classi-promass or prostas before a cella. [< Gk PEO-\*, STASE]

mos'tat), Anat —odj. 1. Also, pros'table
of or pertaining to the prostate gland. —n.
ste gland. [1840-80; < NL prostata < Gk
standing before. See PRO-3, -57AT]

to-my (pros/to tek/to mc), n. pl. -mies.
on of part or all of the prostate gloud.
statt + -ectomy]

land, Anat an organ that surrounds the less of the bass of the bladder, comprising a man, which controls the release of urins, ar portion, which secretic an alkaline fluid in part of the somen and cuhances the ertility of sperm. [1830–40]

Viricle, Anat a small pouch near dithat opens into the urothra. [1920-25]

(pros'to tiz'sm), n symptoms of prosess, obstructed urination, suising from beant or chronic disease of the prostate 1900; prostate + -EM)

i (pros/to ti/tis), n. Pathal. inflammation = gland. [PROSZATE + -1718]

n (pro stir'nam), n. pl -na (-ne), -nums. lerite of the prothorax of an insect. [16:0-P20-', STERNUM] —pro-ster'nal, odj.

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spectrus carefully. 2 a brachure of other bing the major features, attractions, or institution of being sections, or institution of being sections, or institution of being sections.

pros-the-tist (pros-th) tist), n. a person skilled in making or fitting prosthedic devices. (1900-05; prostretices) + -isri

prosethion (proseths on), a Cranion the most forward projecting point of the anterior curface of the upper jaw, in the midsagittal plane. (1820-25; < Gk prosthion, neut. of prosthios frontal, akin to prosthen forward prosethen/io, adj.

prosetto-donetics (pros/the don/tiks), n. (used with a ringular u.) the branch of dentistry that deals with the restoration and maintenance of oral function by the replacement of missing teeth and other oral structures by artificial devices. Also, prosettio-donetis (pros/the-don/sha, -sha s). [1945-60; prosetticists) + -opont + -tcs]

pros-the-don-tist (pros/the don/tist), n. a specialist in prosthodontics. [1915-20; PROSTHODONT(ICS) + -157] Pros-tie (pros-tš), n. Slang. a prostitute. [PROS-T(HUE) + -IE]

Pro-stig-min (pro stig/min), Pharm., Trademark, & brand of neoerigmine.

brand of necesignine.

Prostitute (prostituol/, -iyosi/), n. v., -tut-ed, -tuting. —n. 1. a woman who engages in sexual intercourse
for money; whore, hariot. 2. a man who engages in sexual acts for money. 3. a person who willingly uses his or
her taleat or shifty in a base and unworthy way, usually
for money. —u. 4. to sell or offer (oneself) as a prostitute. 5. to put to any base or unworthy use: re prostitute
one's talents, 1620-30; < L pristitute, n. use of fem. of
prostitutus, ptp. of prostituers to expose (for sale), equiv.
to pro-recol+ stiff, comb. form of var. s. of statuers
to cause to stand + -tus ptp. suffix, see status]
—prostitution, n.
—Syn. 1. call girl, streetwalker, courtesan; trollop,
strumpet.

pros-ti-tu-tion (pros/ti too/shom, -tyoo/-), n. 1. the act or practice of engaging in sexual intercourse for money. 2 base or unworthy use, as of talent or ability, [1545-55; < IL prostitution- (a. of prostitutio). See PEOS-TITUTE, -ION

pro-sto-mj-ate (pro sto/me at/), odj. having a pro-stomium. [1885-90; PROSTORI(UM) + -ATE<sup>1</sup>]

pro-sto-mi-um (pro sto-ms em), n., pl. -mi-s (-ms e), the unsegmented preoral portion of the head of extain lower invertebrates. [1865-70; < NL < Gk prostomion mouth. See PRO-3, STOMA, JUM] —pro-sto-mi-sl, adj.

pro-sto-on (pro sto'on), n. pl. -sto-a (-ato'a), (in classical architecture) a portico. ( < Gk prostoon; see pro-2, FTOAL

prostrate (prostrat), u. trated, trating, adj.—at 1. to cast (queself) face down on the ground in humility, submission, or adoration. 2. to lay flat, as on the ground. 3. to throw down level with the ground. 4. to everthrow, overcome, or reduce to helplessness. 5. to reduce to physical weakness or exhaustion.—adj. 6. lying flat or at full longth, as on the ground. 7. lying flat or at full longth, as on the ground. 7. lying flat or at full longth, as in tokes of humility, submission, or adoration. 8. overthrown, overcome, or helpless a country left prostrate by notural disosters. 9. physically weak or exhausted. 10. submissive. 11. ut. terly dejected or depressed; disconsolste. 12. Bot (of a plant or stem) lying flat on the ground. [1350-1400; [adj.] ME prostrot < L prösträtus, ptp. of prosternere to throw prone, equiv. to prostrates. \*\* title.\*\* vur. s. of sterhers to stretch out + -tus ptp. suffix; (v.) ME prostraten, early, of the adj.]—prostrates (prostrate, adj.)—prostrates, supius, recumbent.

Syn. 6. prone, supine, recumbent

pros-traction (pro stratahan), n. 1. the act of pros-trating. 2. the state of being prostrated. 3. extreme prostruction (pro strainsh), n. z. the act of prostrating 2, the subto of being prostrated. 3. extreme mental or emotional depression or dejection: nervous prostrution. 4. extreme physical weakness or exhaustion: heat prostration. (1,520-30; < LL prostration. (a. of prostration a lying probe. See FROSTRATE, -ION]

pro-style (pro-stil), Archit. —adj. 1. (of a classical temple) having a partice on the front with the columns in front of the antae. —n. 2. a prostyle building or portice. [1690-1700; (adj.) < 1. prostyles < Gk prostyles with pillars in front, equiv. to pro- pro- + styles - styles (n.) < Gk prostyles (n.)

pros-y (pro/zē), adj. pros-l-er, pros-l-est 1 of the nature of or resembling prose. 2 prosnic dull, bedious wearisome, or commonplace. [1805-15, vrose + -r']
-pros/l-ly, adv. —pros/l-ness. 7.

pro-syl-lo-giam (pro sil/o jiz/em), n. Logic. a syllo-giam the conclusion of which is used as a premise of un-other syllogiam; any of the syllogisms included in a poly-syllogiam except the last Cf. optayllogism. [1575-85; < ML prosyllogismus < Gk prosyllogismus. See PRO-, SYL-

See PROTO-, ANTAGONIST] -- Pro-tag/o-nism, n.

Pro-tag-o-ras (pro tag/er ca), n. c480-c421 a.c., Greek Sophist philosopher. —Pro-tag-o-re-an (pro-tag'e re/so), adj. —Pro-tag/o-re/an-ism. n.

prot-a-mine (pro'ts men', pro tam'in). h. Biochem. any of a group of arginine-rich, strongly basic proteins that are not coagulated by heat, occurring primarily in the sparm of fish. [1870-75; PROT- + AMINE]

prot-3-norm-8-ly (prot's om's is). Ophthalm a defect of vision characterized by a diminished response of the relna to red. [1935-40; reot + ANOMACT] —prot's owner's lous, adj.

Pro-ta-no-pi-a (provn 5/p5 s), n. Ophthalm. n defect of vision in which the retlina fails to respond to red or grean. [1900-05; < NL; see Phot-, AN. - . -OPIA] — pro-ta-nop-ic (provn op/ik), ad.

ta-nor-ic (prot/n op/ik), adi.

prot-a-sis (prot/e sis), n., pl. -des (-82/). 1. the clause expressing the condition in a conditional sentence, in English usually beginning with if. Cf. apodosis. 2. the first part of an ancient drama, in which the characters are introduced and its subject is proposed. Cf. catastrasis, catastrophe (def. 4), epitasis. 3. (in Aristotelian logic) a proposition, esp. one used as a premise in a syllogism. [1610-20; < Li.: introduction in a drama < Ck. protessis proposition, lit., a stretching forward, equiv. to pro- Fao. + tosis a stretching (tn-, verbid s. of keinsis to stretch + -sig -sis)] to stretch + sig -518)]

pro-te-an (pro-te en pro te/-), adj. 1. readily essuming different forms or characters; extremely variable. 2. changeable in shape or form, as an amocha. 3. (of an actor or actress) versatile; able to play many kinds of actor or actress) versatile; able to play many kinds of actor or actress. roles. 4. (cap.) of pertaining to, or suggestive of Pro-teus. [1690-1600; Prote(UR) + -AN] —pro/te-sm-tem. n.

pro-te-ase (pro-te az/, -az/), n. Biochem. any of a group of enzymes that catalyze the hydrolytic degradation of proteins or polypeptides to smaller amino acid polymers. [1900-05; prots(in) + -ase]

polymers [1900-05; provis[m] + -ass]

pro-tect (pre telet), c.t. 1. to defend or guard from attack, invasion, loss, annoyance, insult, ctc.; cover or shield from injury or danger. 2. Econ. to guard (the industry or an industry of a nation) from foreign competition by imposing import duties. 3. to provide funds for the payment of (a draft, note, etc.) —u.t. 4. to provide, or be capable of providing, protection: a floor wax that protects as well as shines. (1520-30; < 1 providents, ptp. of protegers to cover in front, equiv. to pro-pro-tect, and fager to cover (akin to tooa, tratten) + -tus ptp. anfix! —pro-tect/s-bit/-ty, n.

—Syn. 1. screen, shelter. See dofend. —Ant. 1. st-tack.

pro-tect-ant (pro tek/tent), n. a substance, as a chemical array, that provides protection, as against insects, frost rust, etc.; protective agent. [1680-70, for an earlier sense; Pauleur + ANT]

pro-tec-tee (pro/tek te/, pre tek-), n. a person, as a head of state, for whom official protection is provided. [1595-1605; PROTECT + -EE]

protecting (pro tek/ting), edj. providing protection or shelter. [1620-80: PROTECT + -ING\*] —pro-tect/ing-ly, edv. —pro-tect/ing-ness, n.

pro-tec-flott (pre tek/shan), n. 1. the set of protecting or the sate of being protected; preservation from injury or harm. 2. a thing, person, or group that protects: This vaccine is a protection against disease. 3. patronage. 4. Insurance coverage (def. 1). 5. Informal a money paid to racksteers for a guarantee against threatened violence, b. bribe money paid to the police, politicians or other authorities for overlooking criminal activity. 6. Econ. protectionism. 7. a document that assures safety from horm, delay, or the like, for the person, persons, or properly specified in it. 8. Archoic a document given by the U.S. customs authorities to a soilor traveling abroad certifying that the holder is a citizen of the U.S. (1275-1235; ME protectio(v)n < LL protection. (a. of protectio) a covering in front. See Protect. -10N — pro-

tec'tion-ai, adj.
—Syn. 1. security, refuge, safety. 2. guard. defense, shield, bulwark. See cover. 3. aegis, sponsorabip, 7.

pro-tec-tion-ism (pre-tek/she niz/sm), n. 1. Econ. the theory, practice, or system of fostering or developing domestic industries by protecting them from foreign competition through duties or quotes imposed on importations. 2. sny program, policy, or system of laws that seeks to provide protection for property owners, wildlife,

conclist Promunciation mer. set, cape, dare, part act, squal; if, ies; os, sver, arder, oil, book, boot, out up, dree, child; sing; shoe; thin, they sh as in treasure a = a as in alone, e us in system, i as in swite, u as in circux. \* as in fire (fi'r), hour (ou'r), l and n can serve us syllable commonants, as in credie (bried'i), and button (but's). See the full key inside the front cover.

ďj. ij, v adi. 53n, adj., n.

pro/-0-ri-en/tal, adj., n. pro-or/tho:dox/, adj pro-or/the-dex/y, edj. pro-pacil·fism, n. pro-pac/l-fist, n., edj.

pro-Pan/a-ma/, edj. pro/-Pan-a-ma/nJ-an. adj., n. pro-pa/pist, n., adj., n. pro-Par/a-guay/, adj., n. pro/-Par-a-guay/an, adj., n.

pro/pa-tri-ot/ic, odi. pro-pa/tri-ot-lam, r. pro-pa/tron-age, adj. pro-pay/ment, adj. pro-Pe-ru/vi-an. adj., n.

pro-Philip-pine/, adj. pro-Pol/ish, adj. pro-politics, adj. pro/-Por-to-guese/, adj., %, PL -Ruese.

## protective

the environment, etc. [1855-60; protection + - - protection-ist, n., adj. - protection-istic, a

pro-tec-tive (pro-tek-tiv), add. I having the quality or function of protecting a protective covering. 2 tending to protect. 3. Econ. of pertaining to, or designed to favor protectionism: protective tariffs. 4. defendive (def. 4). [1656-65; prompt + -vr] —pro-tec-tive-nests. n.

protective coltoid. Physical Chem. a lyophilic colloid added to a lyopholic sol to leasen its sensitivity to the precipitating affect of an electrolyte. [1905-10]

protective coloration, coloration or anything likened to it that eliminates or reduces visibility or conapicuousuess. [1890-85]

protective custody, detention of a person by the police solely as protection against a possible attack or repairs) by someone. [1935-40]

protective slope, a clope given to a yard or the like to drain surface water away from a building.

protective system, Econ. protectionism (def. 1).

[1810-20]

pro-tec-tor (pro-tak/tar), n. 1. a person or thing that protects: defender; guardian. 2. Eng. Hist. a. a person in charge of the kingdom during the sovereign's minoring in charge of the kingdom during the sovereign's minoring the period of the Protectorate, held by Oliver Croming the period of the Protectorate, held by Oliver Croming the period of the Protectorate, held by Oliver Croming (1683-56) and by Richard Cromwell, his son (1683-66). [1225-75; < II (ase Protect, -ton); r. MF) protectour < MF) protectorate, diff. pro-tectorate, diff. pro-tectorate of the protectorate of the protecto

pro-tec-tor-site (pro-tec-tor-site). n. 1. the relation of a strong state toward a weaker state or territory that it protects and partly controls. 2. a state or territory so protected. 3. the office or position, or the term of office, of a protector. 4. the government of a protector. 5. of a protector. 4. the government of a protector. 5. (cop.) Eng. Hist. the period (1853-59) during which Olivers and Richard Cromwell held the title of Lord Protector, sometimes extended to include the period of the reatoration of the Rump Parliament (1869-60). [1685-95; 1807EUTOR + -ALE<sup>3</sup>]

PROTECTOR + -ATE pro-tec-to-ry (pro tek/te re), n., pl. -rice, an institu-tion for the care of destitute or delinquent children. [1650-60; provect + -ony\*]

pro-tect-ress (pro tek/tris), n. a woman who guards or defends someone or something; protector. [1560-70; PROVECT(O)R + 128] — Usage. Sec -923.

pro-th-ge (pro-th zhi-, pro-th zhi-), n. a person under the patronage, protection, or care of someone interested in his or her career or welfure. [1780-90, < F, n. use of prp. of proteger to protect < L protegers. See

pro-th-ges (pro-to zhe/, pro-to zhe/). n. a woman under the paironage, protection, or care of someone interested in her career or welfare. [1770-80; < F, fam. of protege paoracal

protein (protein, -tō in), n. 1. Biochem any of numerous, highly varied organic molecules constituting a merous, highly varied organic molecules constituting a mary in the diet of all animals and other nouphotosynthesizing organisms, composed of 20 or more smino acids linked in a genetically controlled linear sequence into other properties of each protein being determined by the side chains of the amino acids and their chemical attachments, proteins include such specialized forms as collaments, proteins include such specialized forms as collaments, proteins include such specialized forms as collaments, proteins include such specialized forms as collaments for immune defense, and surymen for metabolism. 2. the plant or animal tissue rich in such molecules, considered as a food source supplying essential amino acids to the body. 3. (formerly) a substance thought to be the essential nitrogenous component of all thought to be the essential nitrogenous c

providire ase (provid mas/ naz/ -ts i-), r. Biochem. any of a group of enzymes that are capable of bydrolyzing proteins. [1925-30, providir + ABR]

protein coat, Microbiol capaid.

pro-tein-old (pro'te noid, .cs -), n. Biochem. a polymer of amino acids resembling a biological polypoptide but formed shiotically; suggested as a possible intermediate in protein development during primitive earth conditions. [1955-60; protein + -oid]

pro/tein syn/thesis. Biochem. the process by which amino acids are linearly arranged into proteins through the involvement of ribosomal RNA, transfer RNA, meaning RNA and resource RNA and resources. senger RNA, and various enzymes.

ve/), Lotin 1, temporarily, for the time being. 2, tem-

protend (pro tend'), Archaic —u.t. 1. to stretch forforth. 2 to extend in duration. —o.i. 3. to stretch forward. [1400-50; late ME protenden < L protendere to ward. [1400-50; late ME protenden < L protendere to stretch; see [END']

pro-ten-sive (pro ten'siv), adj. Archaic extended in time. [1635-45; < L protending since of the control of the

pro-te-o-gly-can (pro/th o gli/kan), n. Siochem. a marromolecule composed of a polysaccharide joined to a marromolecule composed of a polysaccharide joined to a polypeptide and forming the ground substance of conpetite tame. (1969; paore(m) + -o- + OLYC- + -on, protected tame)

pro-te-ol-y-sis (pro-tiz ol-s sis), n. Biochem, the pre-te-ol-y-sis (pro-tiz ol-s sis), n. Biochem, the pre-te-ol-y-sis into simpler compounds, sa in pre-te-ol-y-sis (pro-tiz = lit-sis), adj. + Lysis = -pro-te-ol-y-sis (pro-tiz = lit-sis), adj.

pro-te-ose (pro-18 6s), n. Biochem. any of a class of soluble compounds derived from proteins by the action of the gratic juices, pancreatic juices, etc. [1885-90; pro-te(n) + -ose ]

protero, a combining form meaning "earlier," "before," "former," used in the formation of compound fore," "former," used in the formation of compound words protect, Also, esp. before a vowel, protect. Cf. gentle from proj. [< Gk, comb. form repr. proteros. comp. formed from proj. see ruo."]

proter-o-type (prot/er a tip/, pro/ter-), n. a primary type. (PROTERO- + TYPE)

Protest-0-20-1C (prot/ar > zō/ik, pro/ter-). Geol.

Protest-0-20-1C (prot/ar > zō/ik, pro/ter-). Geol.

—adj. 1. noting or pertaining to the latter half of the
Precumbrian Era, from about 2.5 billion to 570 million
Precumbrian Era, from about 2.5 billion to 570 million
Precumbrian Era, from about 2.5 billion to 570 million
Precumbrian Era, from about 2.5 billion to 570 million
Protestor Control of the protest of the protest of the protest of the control of geologic time or the rock systems formed
then: Algorithm. See table under geologic time. [1905—
10. Protesto - 200 + -10]

10. PROTERO. + ZO. + -IC]

Protest (n. protest, v. pra test), protest), n. 1. sn expression or declaration of objection, disapproval, or dissent, often in opposition to something a person is powerless to prevent or avoid: a protest against increased texation. 2. Com. 3. a formal notarial certificates statesting the fact that a check, note, or bill of exchange has been presented for acceptance or payment and that it has been refused, b. the action taken to fix the liability for a dishemared bill of exchange or note. 3. Late. 3. (upon one's payment of a tax or other state or city exaction) a formal statement disputing the legality of the demand. 5. a written and attracted declaration made by the master of a ship stating the circumstances under which some damage has happened to the ship or camplaint made to an official.

—u. 5. to give manifest expression to objection or disputing the master of a ship stating the circumstances.

complaint made to an official.

—u.i. 5. to give manifest expression to objection or dispersion in the complaint made to an official.

—u.i. 5. to give manifest expression to objection or disapproval; remonstrate. 6. to make a protest or remonstrance declaration.

—u.i. 7. to make a protest or remonstrance against; object to. 8. to say in protest or remonstrance against; object to. 8. to say in protest or remonstrance or to make a formal declaration of the uonacceptance or no make a formal declaration of the uonacceptance or no make a formal declaration of the uonacceptance or no make a formal declaration of the uonacceptance or no make a formal declaration of the uonacceptance or no make a formal declaration of the uonacceptance or no make a formal declaration of the uonacceptance or no make a formal declaration of the uonacceptance or no make a formal to protest or the uonacceptance or no make a formal to protest or the uonacceptance or no protest or protest or protest or protest or protest or no protest or protest or no protest or no

See deciare. — Art. 1. approval. 5. approve.

Protessizant (prot/s stant or, for 4, 6, pre tes/tent), n.

1. my Western Christian who is not an adherent of a Catholic, Anglican, or Eastern church. 2 an adherent of any of those Christian bodies that separated from the any of those Christian bodies that separated from the group descended from them. 3. (originally) any of the group descended from them. 3. (originally) any of the group descended from them. 3. (originally) any of the group descended from them. 3. (originally) any of the Brief princes who protests against the decision of the Diet of Speyer in 1529, which had denounced the Reformation. 4. (i.e.) a person who protests. —adj. 5. Reformation. 4. (i.e.) a person who protests. —adj. 5. (i.e.) protesting. (1530-40: < G or F, for L protestantes p. 1 of protestantes p. 1 of protestantes p. 1 of protestantes p. 1 of protestantes. See puotes 7. —ANT)

Prot/estant Epis/copal Church/. See Episcopal Church in Amorica.

Prot/estant eth/ic. See work ethic. Also called Prot/estant work/ eth/ic. [1925-50]

Protestantism (proto stan tizom), n. 1. the religion of Protestant 2 the Protestant churches collectively. 3. adherence to Protestant principles. [1540-50; PROTESTANT + -1574]

Protestant Tems (protestantize), v.t., -ized, -iz-ing. to conform to Protestantiam. Also, to conform Protestantiam. Also, esp. Brit., Protestantiam. (1825-35; Protestant + -ize)

Prot/estant Reforma/tion, reformation (def. 2). prot-as-ta-tion (prot's sta'shen, pro'ts-, -tc-), n. 1.

prot-as-ta-tion (prot's sta'shen, pro'ts-, -tc-), n. 1.

the act of protesting or affirming. 2 a scient or earthe act of protesting or affirmation. 3. formal expression or

Prote-us (prots 38, -t) god, son of Oceanus and assume different forms a assume different forms at thing that readily change ples, etc. 3. (La.) Soctor serobic bacturia of the g as pathogens in the gas tracts of humans.

pro-tha-la-mi-on (DF end-a (-m\$ o). a song ( marriage [1597; PRO-mund Spenser]

pro-tha-la-mi-um (p (-mē =) prothalamion.

pro-thal-li-um (pro (chalfe), 1. Set the plants 2. the analogo seed-bearing plants. (it the light the ligh

pro-thal-lus (pro thal prothallium. [1850-55; protines is (proth/s :

1. the addition of a sou
a word, as in Spanish
2. Eastern Ch. a. Also tion and preliminary ments. b. the table on ments. b. the tank on the sanctuary or bema cap.) Gk. Antig. a rem in state. [1665-75; < fore. See FEO. 2. THESE —pro-thet/leady, or

pro-thon-o-tar-y (p pro-thom-o-tary p. pl. enr-les. 1. s courts of law. 2. Ro members of the col charged chiefly with canonizations. b. an prolates. 3. Gk. Orth fiorch of Constanting late M2 < MI. profits protonomics. See Fe al (pro thom/s tarys: see thour/o-tarys) approximation.

prothon/otary ap ostalic. a member c Roman Curia. [1545 protion/otary was taris citres, of the ex-head and underpart [1780-90, Amer.: 80 bles the robes tradit

glands in the enteric to promote the seri prothorac/i hood. [1885\_90]

pro-tho-rax (pro to tho-ra-ces (-thor's of the thorax of an (1820–30; < NL; & (pro-tho-ras-ik, -th pro-throm-bin (p protein involved in by factors in the p called thromboger pro-tist (pro-tist).
isms, classified in
free-living or aggr bave diverse repro ing the protozonal the more primitive distribute the orga and Animalia sa [1885-90; < NL P < Gk profisios (i protos first; see Ps n.—pro-tis/tic,

Pro-tis-ta (pro t a taxonomic king < NL; see Provis pro-tis-tol-o-gy Protists. [1910-1 to-log-i-cal (pro gist.

pro-ti-um (pro/ and most corner [1930-35; prov.

proto-, a combi
"earliest form o
words (protomor
in chemical term
compounds, or t
of an element. I comb. form repr

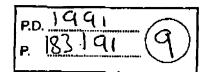
pro-to-ac-tin-i protectinium

## APPENDIX II

## Copy of Reference

## Sara et al.

The Biological Role of Truncated Insulin-like Growth Factor-1 and the Tripeptide GPE in the Central Nervous System



## XP-000917411

The Biological Role of Truncated Insulin-like Growth Factor-1 and the Tripeptide GPE in the Central Nervous System<sup>a</sup>

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Companyons of Neutron beginning

Department of Neuroendoctivology Institute of Anatomy University of Zwrich Zwrich, Switzerland

## INTRODUCTION"

Since early in this century, attempts have been made of denilty substances present in scrum and organ extracts that are capable of promoting the growth of the nervous system. Today several such growth promoting factors have been isolated and identified, such as nerve growth factor (NGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and insulminke growth factors (IGFs). It has become clear that these growth factors are endogenously produced within the developing allowing specific growth phases and that they interact to regulate the growth and developing of the central nervous system (CNS). A role for the IGFs in the regulation of the central implicated 20 years ago by the finding that growth hor bose backers indirect action on growth which was believed to be mediated by the production of a brain growth factor from either the placents or the fetus.<sup>12</sup>

These studies have been supported by the Swedish Medical Resemble Control Osternam Fund, Swedish Cancer Foundation, and the Cancer Fundin Street John 184

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## TRUNCATED IGF I AND GPE

A bioassay to determine fetal brain scall DNA synthesis and later a radioreceptor assay using fetal brain plasma-membranes were developed to isolate the brain growth factor from human fetal brain listue. Partial amino acid sequencing revealed the brain growth factor to be idequical to IGF-1 over the first 29 amino acids, but to have a truncated aminoterminus facting the first three amino acids of IGF-1 (FIGURE 1). The carboxy terminal amino acid was shown to be identical to that of IGF-1. An identical truncated IGF-1 was subsequently instead from the adult human brain. Intact IGF-1 could not be detected in either the fetal or the adult human brain. The formation of truncated IGF-1 or INIGF-1 appeared to be specific to the tissue extract since only intact IGF-1 was isolated from serum when the same purification process was used.

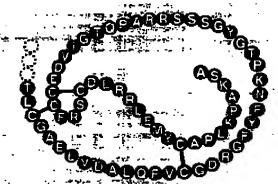


FIGURE I. Amino acid sequence of human truncated IGF-1 (-IN:IGF-1). The single letter unimo acid code is used. The protein lacks the aminotecrainal tripeptice GPE. Truncated IGF-1 has been identified in human braig, busing platelets, porcine uterus, and hoving colostrum.

The possibility of further structural modifications in the brain IGF could not be discounted at that time since the purified peptide displayed greatly enhanced neurotrophic activity compared to IGF-1. The complete amino acid sequence of the peptide has now been deduced from the nucleotide sequence of human fetal brain IGF-1 cDNA? Using reverse transcriptiant polymerase chain reaction (RT-PCR) to amplify cDNA obtained from included human fetal brain, two cDNA sequences encoding precursor proteins that correspond to IGF-1a and IGF-1b were obtained. Thus the amino terminal truncation of the IGF-1 protein represents the only sequence difference in the brain IGF-1 (Fiction 1). The brain truncated IGF-1 must likely arises from posttranslational modification of the IGF-1 procursor protein. As yet it is unclear as to whether the precition to truncated IGF-1 is the a or b form of the IGF-1 probormone. Recently, the aimmo terminal tripeptide of IGF-1, namely, glycyl-probyl-glutamate (GPE), has been identified in human brain. Thus there are two protein products from expression of the IGF-1 genc in the human brain, namely, truncated IGF-1 and the tripeptide GPE.

SARA a al.: TRUNCATED IGF-1

The presence of IGF-1 in the nervous system appears to be a phylogenetically. ancient phenomenon. Using immunological methods, IGF-1 has been localized in the nervous system as well as the gut of lower vertebrates, including bony and cartilaginous fish and cyclostomi, as well as protochordates. For example, IGF-1 immunoreactive perikarya and fibers have been observed in all levels of the brain of the Atlantic hagfish, Myzine glumosa. IGF-1-like immunoreactivity has also been localized in central neurones of the wrochordate Ciona intestinalis and the cephalochordate Branchiostoma lanceolatum. Thus the presence of IGF-1 in the "train gut ans" has been well preserved during venebrate evolution. The identity of the IGF-1-like molecule in the brain-gut axis of the lower vertebrates and projection dates remains to be determined. The nucleotide sequence of an IGF cDNA sidiates from Myaine glutinasa showed 70% homology to the A and B domains of both human IGF-1 and IGF-210 and a hybrid insulin/IGF cDNA related to both hurrien man and IGFs has been closed from Branchiostoma californesis. Chan and proposed that the latter bybrid molecule represents the transitional form prior to insulin and IGF divergence at an early stage of vertebrate evolution. It is sple that the deduced amino acid sequence of the hybrid insulin/IGF molecule revents a different aminoterminal dipeptide compared to mammalian IGF-1. A plasme mem-

brane receptor similar to that of mammalian IGF-1 receptor has also been identified, in the nervous system of lower vertebrates, including Myzine glatinosa. The truncated IGF-1 has been identified in several tissues (FIGURE 1). Ogasawara et al identified truncated IGF-1 in purcine uterus where the peptide accounted for the complete mitogenic activity of uterine extracts. 13 Trumsled IGF-1 has also been isolated from human platelets." Lysates of human platelets contain intact as well as truncated IGF-1 and IGF-2. IGF-1 was released from the placelets during degranulation, suggesting a role in wound healing.15 Francis et 41 have identified truncated IGF-1 in bovine colostrum where intact IGF-1 was additionally found to be present. 16 In all studies during its purification, truncated IGF-1 displayed enhanced biological activity. With the availability of synthetic and recombinant, truncated IGF-1, the reason for this enhanced biological potency became apparant. Truncated IGF-1 binds only weakly to the IGF binding proteins (IGFRPs).17 Although truncated IGF-1 shows some binding to IGFBP-3, a marked reduction in binding affinity to IGFBP-1, -2, -6 has been found in comparison to intact IGF-1 (le than 1%). Analogues of IGF-1 with substitutions in the aminoterminus pentapeptide. have identified Giu in residue 3 as playing a significant role in IGFBP binding. In a wide variety of cultured cells, it has been demonstrated that the enhanced piologic activity of the truncated IGF-1 is most likely due to its failure to be bound by IGFBPs which can compete with the IGF-I receptor and attenuate the biological activity of IGF-1. Thus the failure to bind to IGFBPs results in a greater availability of truncated IGF-1 to the target cell receptors (FIGURE 2).

## **BIOLOGICAL ACTION IN CNS**

Truncated IGF-1 (-3N:IGF-1) and the tripeptide GPE display separate biological functions in the nervous system which are mediated via distinct receptors on their target cells. Truncated IGF-1 has a potent neurotrophic action via interaction in the IGF-1 receptor in the CNS. The IGF-1 receptor is widely distributed throughout the CNS, and its expression is enhanced during the rapid growth phase of early life. The IGF-1's neurotrophic action predominates during early development, when the IGFs-1 regulate the growth and differentiation of the nervous system. In vino scudies have demonstrated that IGF-1 stimulates the proliferation of neuroblast and glioblast

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FIGURE 2. Model to arround for the classical activities of truncated IGF-1 compared to initial IGF-1. Failure to believe surplated with the IGF-9r as hypothesized to result in greater availability of truncated IGF-1 receptors on target cells.

precursor cells, as well as their differentiation. If Several studies indicate that IGF-1 may play an important riple in synapse formation and myelination. In the presence of the various IGEs may be formation and myelination. In the comparison neurotrophic activity compared to indicate formation IGF-1. Using feigl brain cells in neurotrophic activity compared to indicate IGF-1. Using feigl brain cells in the contract of the culture medium-could that this command neurotrophic potency was to be a failure of troncated IGF-1 for bind to handing proteins. The addition of synthesis by intact IGF-1 but had no effect by the action of truncated IGF-1 had a potent by the action of truncated IGF-1 had a potent growth promoting action on parietal cortex and spinal cord grafts transplantically be appreciately the action of truncated IGF-1 had a potent growth promoting action on parietal rats. This in vivo model allows for direct observation of graft surgical and growth. The action of truncated IGF-1 was formation of grafts and growth of the eye of adult action of truncated IGF-1 was formations as the stage of receptor maturation; and provide that these differences reflected the stage of receptor maturation; and inspirate maturation in the various regions. This is in discrete times during CNS development of the presence of IGFBPs which were present in the vitrous fluid.

Similarly, when administered amayeriently, truncated IGF-1 displays reduced binding to IGFBPs in the control among the following the control among the contr

### SARA & AL: TRUNCATED ICF-1

from the blond? and is also degraded (aster than intact IGF-1.31 Consequently, the acute hypoglycemic effect of truncated IGF-1 is greater than that of intact IGF-1.3 Increased degradation due to low association with IGFBPs most likely explains the failure to observe any significant enhancement in growth following the subcutaneous administration of truncated IGF-1 to neonatal rats in spite of enflancement limits observed following intact IGF-1 administration. In contrast to the growth discount rats, enhanced growth has been observed in growth-hormone-deficient highly mount following truncated IGF-1 administration. Thuncated IGF-1 has similarly been reported to be more potent than intact IGF-1 in regulating nitrogen balance and muscle protein metabolism in nitrogen-restricted rats.

The antinoterminal tripeptide of IGF-1, GPE, displays a different range of biological actions compared to transated IGF-1. These effects are not mediated by IGF receptors. As shown in FIGURE 3, GPE falls to cross-react in the IGF-1 receptor and does not influence the binding of either intact or invincibility of IGF-1 receptor. The tripeptide similarly falls to cross-react in the IGF-2 receptor. The tripeptide similarly falls to cross-react in the IGF-2 receptor. The tripeptide similarly falls to cross-react in the IGF-2 receptor. The does not bind to IGFBPs nor does it influence the association of the IGF-1 in the indiring proteins. Extensive in vivo studies have not revealed any growth-prompting activity of GPE. The results of one such study are summarised in Intellige 4. Growth was followed in rats receiving 30 µg GPE subcutaneously (sc) per day from days 3 to 15 of postnatal life. As shown in FIGURE 4, no significant growth effects, including tail length and organ weights, were observed. However at maturity, the unimals receiving GPE during this preweating period displayed a significant increase in softway measurements in an open field test. It has since been demonstrated that GPE plays a neuromodulatory role in the CNS, which may account for the changes in activity observed in the GPE-treated rats.

The structure of GPE suggested that it may interact in receptors for gluramate which is a major excitatory amino acid neurotransmitter in the CNS. Using rift synaptic membranes, it was shown that GPE cross-reacted in the N-methyl-n.

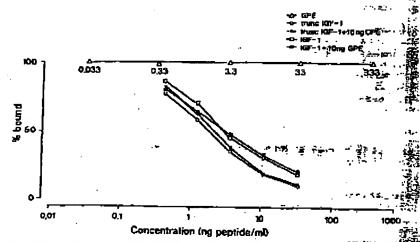


FIGURE 3. Competition with 125-1-1GF-1 for binding to human fetal brain membranes. Dear expressed as the percentage bound in the absence of competing peptide.

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aspartate (NMDA) but not the kajuate or quisqualate type of glutamate receptor. While the carboxyl terminal glutamate was necessary for NMDA receptor binding, the aminotorminal glycine potentiated this crites reaction. Glycine has earlier been shown to potentiate responses ancested with the NMDA receptor and has been suggested to be a specific regulator of the NMDA receptor via binding to an allosteric site. CPE facilitates, the religiously dispersing from cortical sites. As shown by the use of a telective competing altragonist, this action is mediated via interaction in the NMDA receptor is in addition, GPE has a potent stimulatory action on acctylcholine release from control neurones. In This action cannot be inhibited by NMDA receptor blocking agains, and acctylcholine potentiation is mediated via an as yet unidentified receptor. CIL does not interact with choline uptake sites or muscarinic receptor of the potential occurs at a concentration several orders of magnitude greater han that required to potentiate acctylcholine release. Thus the receptor mechanism of acceptorologine potentiation termins to be identified. It had been reported garage that interact of potentiates acctylcholine release from control slice. It sample before him become potentiation termins to be interact for an expension of magnitude greater han that required to potentiate acctylcholine release from control slice. It sample before him become reported to enhance catechol-amine release from chromating the sample before the tripeptide GPE. However, during this acute experiment, significantly less fruncated IGF-1 was taken up by the cortical slices during the 30 minute members are for the sample cortex. It is a control to the cortex of the

rular barrier to directly interact with neutones and induce an acute action.

Neuronal activity can be modulated by GPE. This has been demonstrated in single cortical neurones following logicipharetic application of GPE. As shown in Figure 5, GPE alone has no effect on the electrophysiological activity of the neurone; however, when applied ingether with glutamate, it potentiales the action of

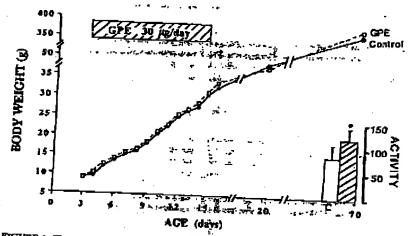


FIGURE 4. The growth of rats receiving either 30 µg GPE sc/day or vehicle alone from days 3 to 15 of postnatal life. No significant effect to body weight was observed. AL70 days of age, open field behavior was examined. GPE-treated pain displayed a significant increase in activity scores.

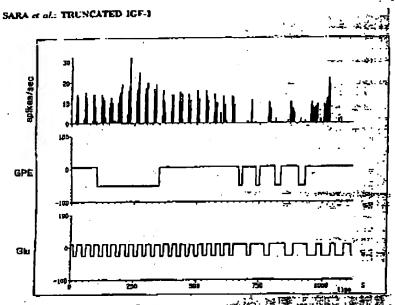


FIGURE 5. Cortical neurone electrophysiological activity following micropographyratic in carlon of GPE. The affect of GPE on sponts neous as well as glutamate-driven single cell act determined as spikes/second is shown.

the glutamate-driven neurone. Similarly, in the spinal cord, GPE has no diremilitance on motor neurone activity when applied intrathetally, however GP potentiates the facilitated spinal cord reflex in response to other simult.

### CONCLUSION

Thus there are at least two protein products from expression of the IGF-1 generative CNS. These proteins result from posttranslational modification of the IGF-precursor protein. Truncated IGF-1 (-3N:IGF-1) acts as a potent occupytophing factor and this action is mediated via the IGF-1 receptor. The tripepine GP-appears to have a quite different CNS function, namely, the modulation of negligible in mitter release. This potentiating action is mediated at least in part via intersection in the NMDA receptor. This is the first example of a product from a growth factor generation in the CNS. A similarly novel role for the neurotransmitter acetylcholine has been suggested in the regulation of brain growth.

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